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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : B04B 5/04, A61J 1/00

A1

(11) International Publication Number: WO 95/01842

(43) International Publication Date: 19 January 1995 (19.01.95)

(21) International Application Number: PCT/SE94/00638

(22) International Filing Date: 28 June 1994 (28.06.94)

(30) Priority Data:
9302369-5 8 July 1993 (08.07.93) SE

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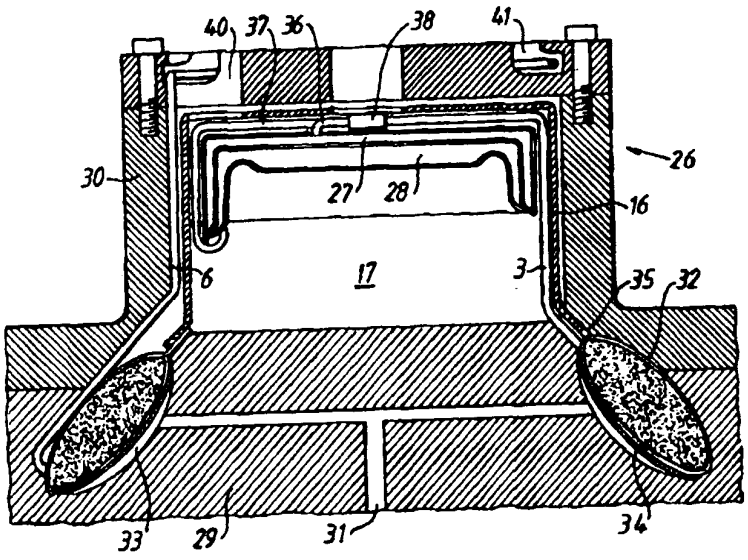
(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: BAG-SYSTEM FOR USE IN CENTRIFUGAL SEPARATION



(57) Abstract

Bag-system for centrifugal separation, comprising an outer, essentially ring-shaped outer bag (1) and a central inner bag (2) which is formed from the central part of the ring and preferably being detachable from the ring, and one or several connnecting channels between the interiors of said bags. According to the invention the bag-system has a rigid, circular centre part (16) on which the outer bag is mounted in a position for centrifugation, whereby the outer bag is given a conical shape around the centre part by means of a ring-shortened contraction of said bag. The inner bag is positioned in a cavity (17) in the centre part, which cavity is arranged to restrict the radial spreading of the inner bag but to allow an axial expansion of the inner bag when it is filled with a liquid. The invention also relates to the use of the bag-system for obtaining thrombocyte suspensions from buffycoat fractions by centrifugal separation and for recovering bone marrow cells from bone marrow suspensions by centrifugal separation.

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BAG-SYSTEM FOR USE IN CENTRIFUGAL SEPARATION.

The invention relates to a bag-system intended for batch centrifugal separation. More particularly the invention relates to a bag-system of the type which comprises an outer, essentially ring-shaped outer bag and an inner bag, formed from the central part of the ring as well as one or more connecting channels between the interiors of these bags.

Systems of coupled bags are used for the centrifugal separation of blood, blood products and other biological fluids. The fluid which is to be separated is supplied to a primary bag of the system and after centrifugation and separation of the fluid into two or more fractions, one or more of these fractions is pressed into the attached bags. For centrifugal separation, specially adapted round and ring-shaped bags are known in this connection. Bag-systems of this type are described e.g. in the international patent applications WO 87/06844 and WO 89/02273. These documents also disclose how this type of bag-system can be manufactured from plastic films which are laid on one another and joined by means of an outer ring-shaped seam and an inner ring-shaped seam, so that a ring-shaped outer bag is formed as well as a plate-shaped inner bag in the central portion of the ring. Several chambers arranged one upon the other can be obtained in the inner bag depending on the number of film layers which are sealed together. The inner seam is suitably provided with a perforation so that the outer and inner bags can be separated from each other.

The fluid which is to be separated is supplied to the outer ring-shaped bag and after centrifugation is subjected to an external pressure which presses the fraction which is closest to the rotor centre through the connecting channel

to the inner bag. Several different combinations of connected channels can occur if the inner bag comprises a plurality of chambers. Different methods are also known for achieving the compressive pressure on the bag whilst this is in the rotor and undergoing rotation.

From a point of view of cost it is advantageous if the inner bag can be manufactured from film material which is obtained from the remaining central portion of the outer bag. If a large volume is required for the inner bag, this means however that the diameter of the outer bag will be large, which is a disadvantage with many applications and requires centrifuges with large rotor diameters.

An object of the present invention is to provide an improved bag-system of the aforementioned type which gives an increased flexibility as regard the choice of the volume of the inner bag and the diameter of the outer bag.

This and other objects and advantages which are described in more detail in the following description, are achieved by a bag-system as defined in the claims.

Thus the bag-system comprises an outer essentially ring-shaped outer bag and an inner bag, formed from the central part of the ring and preferably being detachable from the ring, as well as one or more connecting channels between the interiors of these bags. According to the invention the bag-system further comprises a rigid, circular centre part on which the outer bag is mounted in a position for centrifugation whereby the outer bag is given a conical shape around the centre part by means of a contractive ring-shortening.

The centre part also has the task of facilitating the handling of the bag-system as well as fixing the inner bag in the intended position for centrifugation. The centre part has an inner cavity, in which the inner bag is placed in a way which limits its radial spreading but allows an expansion in the axial direction when it is filled with fluid. The inner cavity has a diameter which is less than the diameter of the inner bag whereby the inner bag is pressed into the cavity so that its peripheral part curves along the walls of the cavity. The centre part preferably has essentially the form of a downwardly-open cylinder.

The contractive ring-shortening of the outer bag can be achieved by a section of the ring being gathered together into a fold. The inner ring-shaped fluid communication in the bag is thereby blocked. The fold can be placed on the ring so that two overlapping bag ends are obtained, as well as a material piece between the bag ends which remains empty and blocked for fluid flow. The outer bag can also be cut and the resulting free ends sealed. The shortening of the bag can then be achieved by drawing the ends together so that they overlap each other. The bag can also be cut in two places and the intermediate material piece removed, whereby the free ends are drawn towards each other in a corresponding manner until they overlap.

Due to the fact that the circle-shaped fluid communication in the outer bag is blocked or interrupted, a flow of the fluid around the bag when the centrifuge accelerates or retards is prevented, which accelerates the commencement of the separation procedure and prevents silting up when the rotor is slowed down.

The separation chamber in the rotor is adapted to the conical form of the shortened outer bag. Due to the fact that the separation occurs in a radial direction in a relatively narrow conical chamber, an angular separation effect and a fast separation are achieved. The separation path in the radial direction is shortly before the specific heavier component meets an oblique surface which leads it to the bottom part of the cone.

A central placement of the inner bag in the middle of the rotor combined with a limited spreading in the radial direction means that the fluid which is taken up in the inner bag is subjected to a limited field of force. This has shown itself to be particularly important when recovering particle suspensions, e.g. thrombocyte suspensions since a re-sedimentation and undesirable aggregate formation of the particles has to be avoided.

The bag-system according to the invention is also particularly suitable for recovery of bone marrow cells by centrifugal separation of bone marrow suspensions.

The invention will now be described in more detail with reference to the accompanying figures.

Fig.1 shows an embodiment of an outer and an inner bag for a bag-system according to the invention.

Fig. 2 shows a partially different embodiment of an outer and inner bag according to the invention.

Fig. 3 shows a cross-section through the rigid centre part for a bag-system according to the invention.

Fig. 4 shows the centre part according to Fig. 3 in horizontal section.

Fig. 5 shows a sectional view through a bag-system according to the invention with rigid centre part according to Figs. 3-4.

Fig. 6 shows the bag-system according to Fig. 5 in horizontal section.

Fig. 7 shows a sectional view through a bag-system with double inner bag chambers, mounted in a centrifuge rotor.

Fig. 8 shows the centrifuge rotor seen from above.

Figs. 9-11 shows schematically the use of a bag-system according to the invention during recovery of thrombocyte suspension.

Figure 1 thus shows an embodiment of an outer, essentially ring-shaped outer bag 1 and a central, essentially circular, inner bag 2 formed from the central portion of the ring. The interiors of the bags are joined with a tube 3 having an orifice 4 in the outer bag and an orifice 5 in the inner bag. The outer bag is provided with an additional connection 6 for supplying and removing of fluid to and from the outer bag. The orifice 4 is placed in a radially inwardly directed bulge 7 of the outer bag. When the lighter enriched phase against the centre of the rotor is pressed out of the outer bag after separation by means of pressure being applied to this, vortex formation can easily

occur around the outlet opening and parts of the next phase can be sucked out. By placing the orifice 4 on a bulge which extends radially further inwardly than the other parts of the outer bag and by forming the rotor so that this part of the bag forms a relatively narrow gap between the rotor and the rotor cover in the height direction, the vortex formation around the orifice 4 can be avoided and the lighter phase can be recovered with high quality and high yield.

The outer bag is further provided with a number of attachment means, e.g. eyelets 8, for attachment of the outer bag onto a stiff centre part, which will be described in more detail with reference to Figs. 4-7.

The bags are produced by two plastic films being placed over each other and sealed together with an outer ring weld 9 and an inner ring weld 10. The latter weld is such that it either separates the bags totally from each other or makes them separable from each other by tearing off.

Fig. 2 shows a partially different embodiment of a bag according to the invention and differs from what has been described with reference to Fig. 1 in that the inner ring weld 10 is somewhat eccentricly placed with respect to the outer. The outer bag is thereby wider in the area of the orifice 4 of tube 3 in the outer bag. This wider portion fulfils the same function as the bulge 7 in the embodiment according to Fig. 1. The wider part of the outer bag is placed in a corresponding manner in the narrow gap between the rotor and the rotor cover. Details which correspond to each other in the figures have been denoted with the same reference numeral. The ring-shape of the outer bag is cut and the thereby resulting free ends 11 and 12 are closed. The cutting can e.g. be carried out by means of a weld which at the same time seals the ends. In the shown

embodiment the outer bag is cut with two substantially radially directed welds 13 and 14 at a certain distance from each other. The intermediate material piece 15 is removed. The essentially ring-shaped outer bag is thus free from any circulating inner fluid communication.

In order to reduce the diameter which is taken up by the bag-system and at the same time facilitate handling of the bags and fixing of these in the intended positions for centrifugation, a rigid circular centre part 16 is used. The outer bag is mounted around the outside of the centre part and the inner bag inside in an inner space 17 in the centre part.

The bag-system can thereby be lifted into and out of the rotor with a simple hand grip. Figs. 3 and 4 show an embodiment of such a centre part in the form of a downwardly-open cylinder. Fig. 3 shows a sectional view through the centre part and Fig. 4 shows the centre part in horizontal section. The cylinder, at its open end, is provided with a conical inclined rim 18, in which the outer bag's inner edge is fastened in the fastening means 19 which cooperate with the fastening eyelets 8 in the outer bag. On its inside the cylinder has holders 20 and 21 for fixing the connection tube 3 between the outer and the inner bag and is provided with openings 22 and 23 for access to the tube from the upper side of the centre part, to allow attachment of clamp valves or optical sensors etc. onto the tube when the bag-system is placed in the rotor.

Figs. 5 and 6 show a complete bag-system with centre part in section and in horizontal view respectively. The inner bag 2 is placed inside the centre part 16, which is arranged to limit the radial spreading of the inner bag but to allow an axial expansion of the inner bag when this is filled with a fluid. In the figures a centre part is shown

in the form of a cylinder according to Figs. 3-4. The cylinder has a smaller diameter than the bag which is pressed into the cylinder so that its peripheral part 25 is folded and rests against the inner surface of the cylinder. When the inner bag is filled it expands in the vertical direction inside the cylinder. The folding of the inner bag's peripheral part, which is the result of it having a larger diameter than the centre part 16, has shown itself to have only a marginal intrusion into the maximum volume which can be taken up in the inner bag.

The outer bag 1 has too large a diameter for its inner edge to fit onto the rim 18. In connection with mounting onto the centre part, the ring-shaped outer bag is shortened by a section of the ring being drawn together into a fold 24 which is laid onto the ring. The continuous fluid communication in the ring is thereby broken. In the case where the ring is cut by a weld or similar, the ring is shortened by the end being laid in overlapping relationship. With the shortening of the ring the bag will assume a conical shape without being folded and can easily be fastened to the conically inclined rim 18 formed in the same way on the cylinder 16. In this way the bag-system has a small diameter and can be used in small centrifuge rotors despite the bags being manufactured with a diameter which is dependent on the volume which the inner bag 2 is desired to have, i.e. the central section of the outer bag.

Fig. 7 shows a section through a bag-system placed in a centrifuge rotor 26 adapted to the system. In this case the bag-system has an inner bag with an upper chamber 27 and a lower chamber 28. Fig. 8 shows the rotor seen from above. 29 denotes the base of the rotor and 30 its cover. A channel 31 for hydraulic fluid passes through the axis of the rotor to the rotor's ring chamber 32 where a ring-shaped hydraulic chamber 33 is delimited from the rest of

the ring chamber by a membrane 34. The outer bag is placed in the ring chamber and its bulging portion 7 is positioned in the gap 35 between the base of the rotor and its cover. The connection tube 3 which has an orifice in the bulge 7 in the outer bag, branches into a branch 36 which has an orifice in the upper inner bag chamber 27 and a branch 37 which has an orifice in the lower. The branch conduits are placed in clamp valves 38 and 39 which are controlled by the programmed operation of the centrifuge and/or photocells which detect the displacement of the boundary surface of the phase in the connection tube 3. The outer bag is connected with an additional tube 6 which is drawn up through the hole 22 in the cassette and further through a hole 40 in the rotor cover. The tube is used for filling of the outer container with the fluid which is to be separated and is thus accessible from the outside of the rotor. After filling of the outer container the tube is closed with tube welding tongs and is placed in a groove 41 in the rotor cover.

Instead of a branched connector tube 3, the outer bag can be connected to each of the chambers in the inner bag via separate tubes and one-way valves in the same way as described in WO 89/02273 and the bag-system is used for washing operations such as described in said document.

The bag-system according to the invention can thus be used for the separation of blood and other biological fluids and with treatment of such fluids with different components. The system with double inner bag chambers and branched connector tube between outer and inner bag can be used when a separation into three different fractions should occur. Two fractions are each led to their respective inner bag chamber and the third remains in the outer bag.

The bag-system according to the invention is specially adapted for recovering thrombocyte suspensions from isolated buffycoat fractions, which is schematically shown in Figs. 9-11. Buffycoat is recovered as an intermediate fraction by centrifugal separation of whole blood. A number of buffycoats 42, e.g. six, are transferred via the tube 6 to the outer bag 1, upon which the tube 6 is cut and sealed with tube welding tongs (Fig. 9). The buffycoats are centrifuged and divided up in a thrombocyte-rich plasma 43 and a remaining volume 44 (Fig. 10). This centrifugation occurs with a certain amount of care in order to avoid centrifuging out of the thrombocyte cells. The conical angulation of the outer bag and the relatively small diameter are thereby a large advantage. A pressure is brought to bear thereafter on the outer bag and the thrombocyte suspension is pressed during on-going centrifugation via the tube 3 to the inner bag 2 (Fig. 11). The inner bag will thereby expand in the vertical direction whilst its radial spreading is fixed by the centre part (not shown).

Since the thrombocyte suspension is transferred to the centre of the rotor and is maintained in a limited area in the radial direction, it will only be subjected to a weak centrifugal force as soon as it is recovered. If the thrombocyte suspension is subjected to a lengthy strong centrifugal force, an undesired aggregate formation occurs and loss of thrombocyte cells. The special requirements which are made for recovery of thrombocyte suspension of high quality and high yield are thus fulfilled by the bag-system according to the invention.

Another field of application where the bag-system according to the invention is especially suitable is bone marrow separation. Bone marrow separation is applied in connection with cancer treatments using large doses of radiation

treatment. Bone marrow is taken out of the patient before the radiation treatment and, through various separations and washing procedures, bone marrow cells are isolated which are re-transfused after the radiation treatment.

A known procedure for isolation of bone marrow cells comprises the following steps:
a) centrifugal separation of bone marrow suspension in three fractions and collecting the intermediate fraction, buffycoat;
b) the buffycoat fraction from step (a) is centrifuged one more time in a separation fluid, commonly Ficoll (product name, Pharmacia Fine Chemicals AB), and an intermediate fraction which contains the collected bone marrow cells;
c) washing of the collected fraction from step (b) for recovery of re-transfusable bone marrow cells.

The bag-system according to the invention can be used in such a process in the following manner:

In step (a) a bag-system with double chambers in the inner bag is used and a branched connection conduit from the outer bag to the inner bags, i.e. of the type which is shown in Fig. 7. The outer bag is supplied with a batch of bone marrow suspension, which via centrifugation is divided up into plasma, buffycoat (comprising the bone marrow cells) and remaining products. Due to the influence of pressure on the outer bag the plasma fraction is thereafter pressed, during on-going rotation, to the first inner bag and thereafter a determined amount of buffycoat to the second inner bag, the remaining products being left in the outer bag.

In step (b) a similar bag-system as in step (a) is used. The separation fluid (Ficoll) is supplied to the outer bag and a suspension of the buffycoat fraction from step (a) is

added carefully so that it forms a layer above the separation fluid. The centrifuge is started slowly so that mixing is avoided. Depending on the specific weight of the cells, they will migrate through the separation fluid or stay above this during centrifugation. The bone marrow cells are enriched in a layer above the separation fluid. The supernate (plasma) is thereafter pressed, during on-going centrifugation, into the first inner bag chamber and thereafter an intermediate fraction consisting of the layer closest above the separation fluid (containing the bone marrow cells) is pressed into the second inner bag chamber. The heavier cell material remains in the outer bag.

In step (c) a bag-system with a single chamber inner bag can be used, i.e. of the type which is described with reference to Fig. 5. The fraction of bone marrow cells loaded with separation fluid from step (b) is transferred to the outer bag and a suitable washing fluid is supplied. After centrifugation the used washing fluid is pressed out into the inner bag. New washing fluid can then be supplied to the outer bag via a tube (such as is shown in Fig. 7) accessible from the outside of the rotor cover and the washing procedure can be repeated as required. The washed bone marrow cells are isolated in the outer bag.

With the bag-system according to the invention a cheaply priced treatment set can be obtained, which allows the separation of biological fluids during on-going centrifugation into separate component containers without the fluids passing complicated, expensive and sterility-unsafe rotating couplings. Despite a small diameter, which can be adapted to an existing centrifuge type, relative large volumes can be taken up in the inner bag. The bag-system is therefore useable for many different types of separations.

CLAIMS

1. Bag-system for use in centrifugal separation comprising an outer, essentially ring-shaped outer bag (1); and a central inner bag (2), which is formed from the central part of the ring and preferably being detachable from the ring; and one or more connecting channels (3, 36, 37) between the interiors of said bags, **characterized** by a rigid, circular centre part (16) on which the outer bag is mounted in a position for centrifugation whereby the outer bag is given a conical shape around the centre part by means of a contractive ring-shortening of said bag.

2. Bag-system according to claim 1, **characterized** in that the outer bag has two free ends, which are formed by cutting the ring and sealing the resulting ends, and that said free ends are wrapped one over the other to shorten the ring when the bag is mounted on the centre part.

3. Bag-system according to claim 2, **characterized** in that the ring is cut in two places and the material section inbetween is removed.

4. Bag-system according to claim 1, **characterized** in that the outer bag is shortened by a fold.

5. Bag-system according to claim 1, **characterized** in that the rigid centre part (16) has a cavity (17) in which the inner bag is positioned and which cavity is arranged to restrict the radial dimensions of the inner bag but to allow an axial expansion of said bag when it is filled with a liquid.

6. Bag-system according to claim 1, **characterized** in that the inner bag comprises two or more compartments (27, 28) arranged over each other, each of them communicating with the outer bag through separate or branched connecting channels.

7. Bag system for use in centrifugal separation comprising an outer, essentially ring-shaped outer bag (1); and a central inner bag (2) which is formed from the central part of the ring and being preferably detachable from the ring; and one or more connecting channels (3,36,37) between the interiors of said bags, **characterized** in that at least one of said channels is connected to the outer bag at a point displaced in the direction against the center of the outer bag compared with the outer border of the inner bag in an embodiment in which the inner bag is defined by a complete circle arranged concentrically in the outer bag.

8. Bag-system according to claim 7 **characterized** in that the outer bag has a radial, inwardly directed extension (7) in which an opening for the connecting channel is situated.

9. Bag-system according to claim 7 **characterized** in that the central part of the outer bag, which is used as the inner bag, is somewhat eccentrically located so that the outer bag is wider on one side and that an opening (4) for the connecting channel is situated at the inner edge of said wider side.

10. Use of a bag-system according to any of the claims 1-9 for obtaining a thrombocyte suspension by centrifugal separation of buffycoat fractions.

11. Use of a bag-system according to any of the claims 1-9 for recovering bone marrow cells by centrifugal separation of bone marrow suspensions.

12. Use of a bag-system according to claim 11, **characterized** in that the separation comprises the steps of:
a) centrifugal separation of bone marrow suspensions into three fractions and utilizing an intermediate fraction, buffycoat;
b) centrifugal separation of the buffycoat fraction from step (a) into three fractions and utilizing a bone marrow-containing intermediate fraction;
c) washing the utilized fraction from step (b), whereby in step (a) and (b) bag-systems are used having two-compartment inner bags (2) and a branched connecting channel (3, 36, 37) between the outer bag and the two compartments (27, 28) of the inner bag.

Fig.1

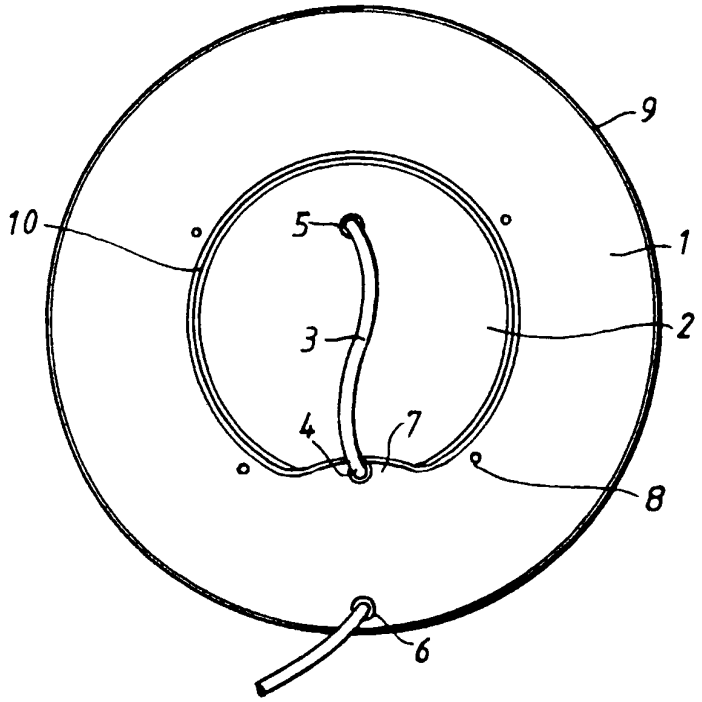

Fig.2

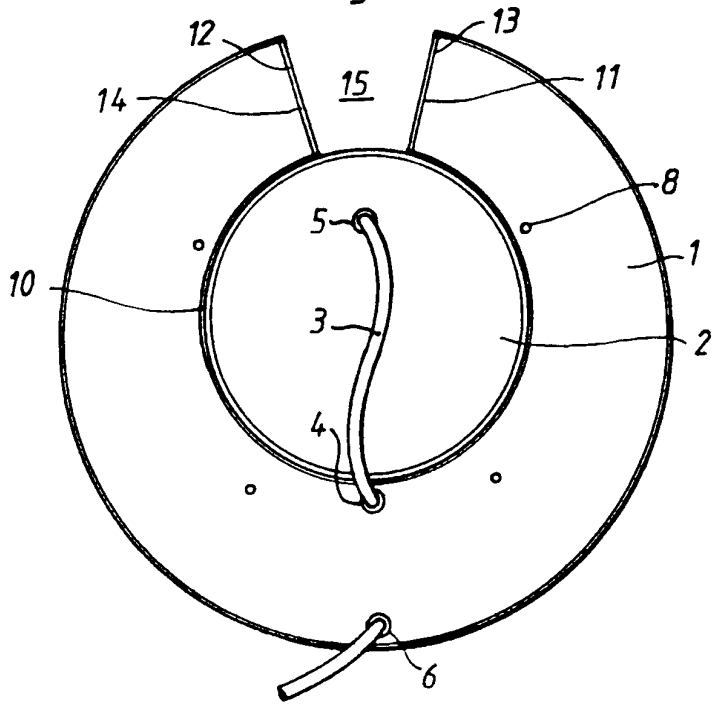

Fig.3

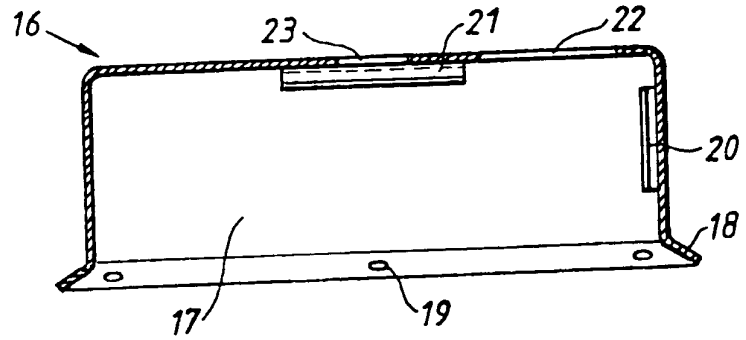

Fig.4

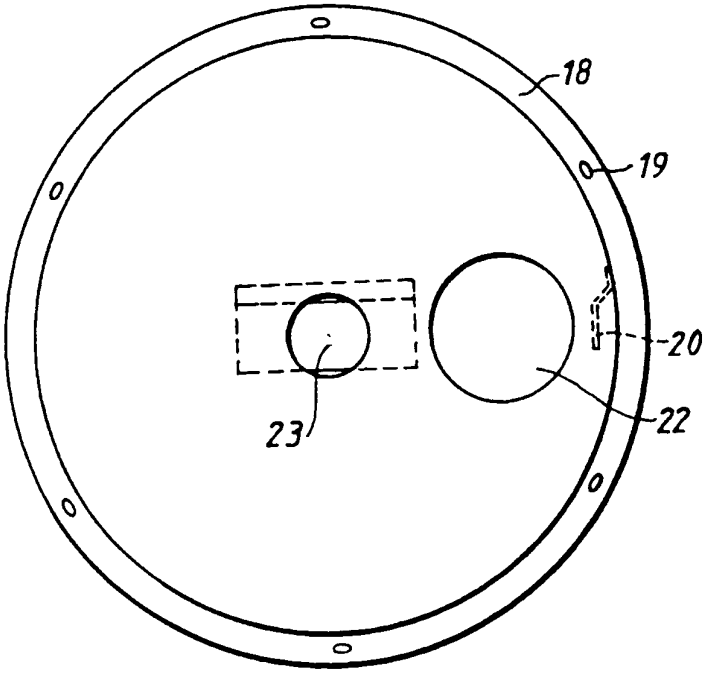

Fig. 5

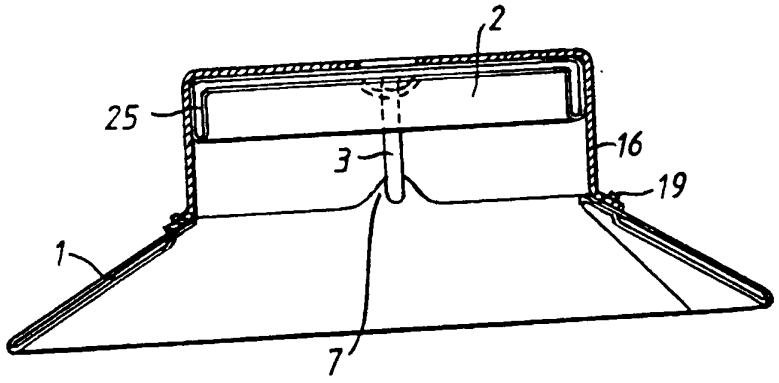

Fig. 6

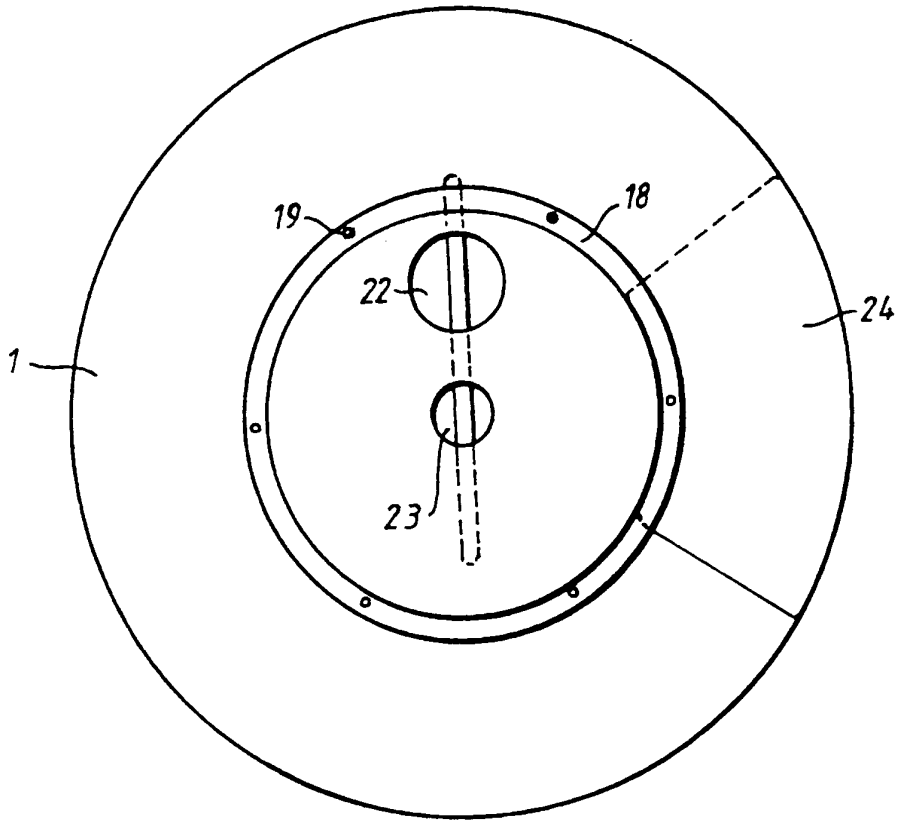

Fig.7

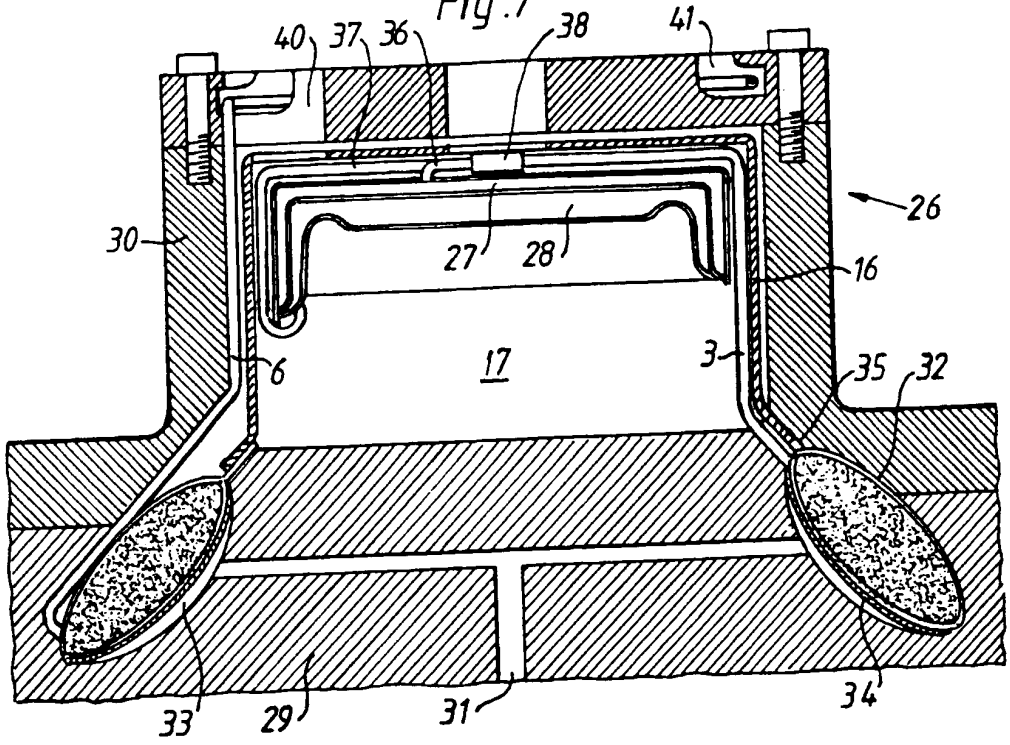
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Fig.8

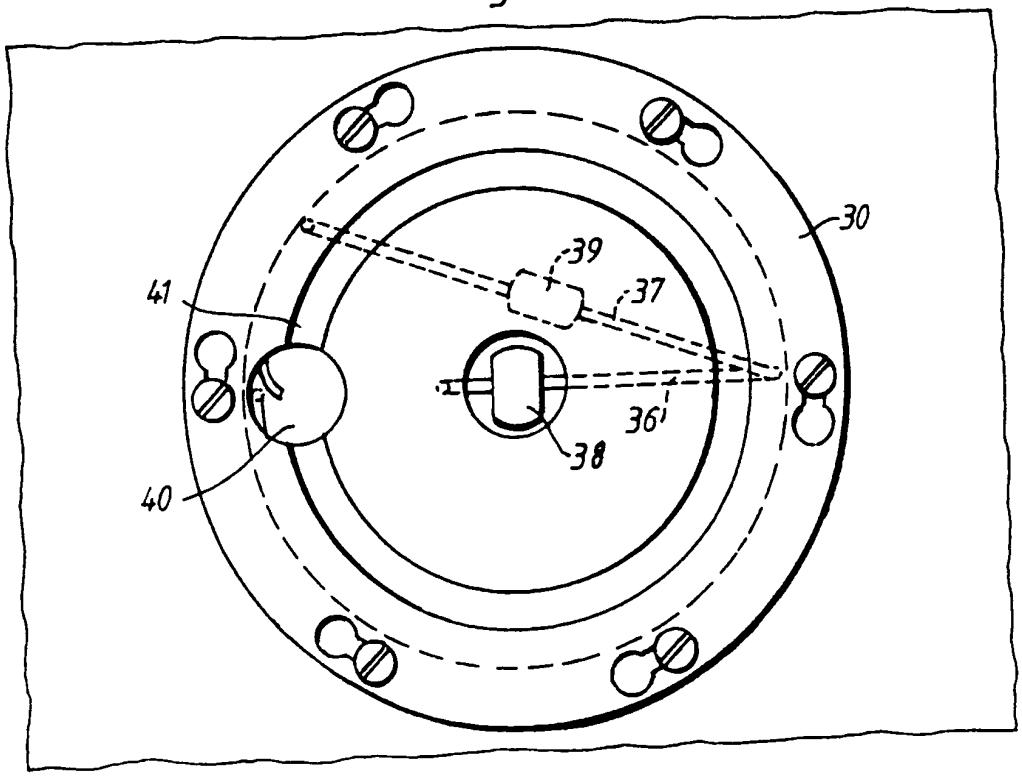
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Fig.9

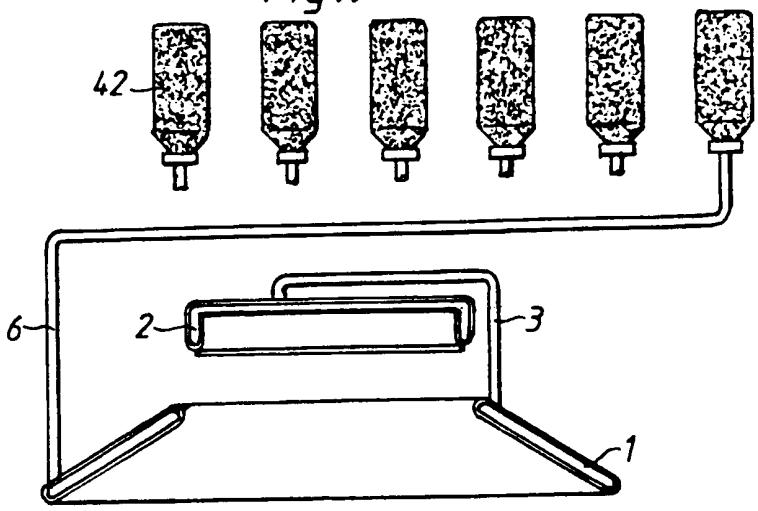


Fig.10

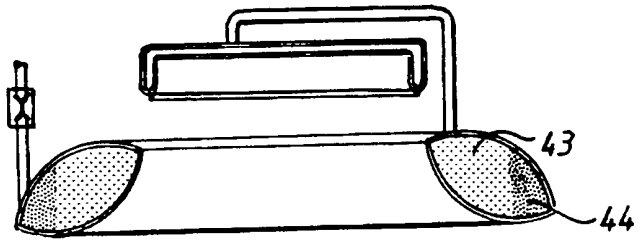
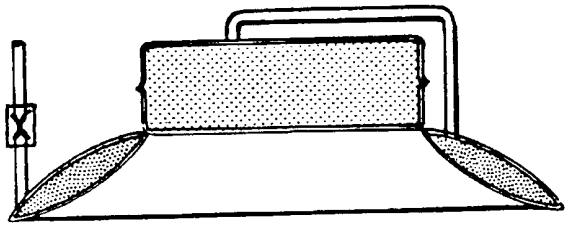


Fig.11



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00638

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6: B04B 5/04, A61J 1/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6: B04B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1994	24 -10- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Johan von Döbeln Telephone No. +46 8 782 25 00

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International application No.
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